REMARKS

This paper is in response to the final Office action mailed on February 5, 2007. Entry and consideration of this amendment is respectfully requested.

I. Status of the Claims

Claims 1-3, 6-19, 23, 24, 26, and 27 are pending.

Claims 4, 5, 20-22, and 25 are canceled.

II. Amendments to the Claims

Claim 1 has been amended to more clearly reflect certain features of the subject hydrophilic polymer-peptide conjugate – namely its ability to transport across the blood brain barrier when administered to the blood circulation. Support for this feature is found in numerous locations throughout the specification and in claim 21, now canceled.

Since this feature was already contained in a pending claim, this amendment should not require any additional searching, nor does it present new grounds for consideration on the part of the Examiner.

Claim 1 has also been amended to recite a particular molecular weight range for the water soluble polymer. Support for the range is found, e.g., in original claim 15 (2,000 daltons), Example 1, Example, 2, Example 4, Example 5, Example 6, and in the specification at page 8, paragraph 0035 (100,000 daltons).

Claim 13 has been amended to conform to the language of newly amended claim 1, since it depends therefrom. Support for a molecular weight of 2,000 daltons is found in the disclosure as described in the previous paragraph.

Claim 14 has been amended to recite polyethylene glycols having certain molecular weights, support for which is found in the specification at the following locations: 2000 daltons (original claim 15), 5000 daltons (page 9, first sentence, Example 5, Example 6), 8000 daltons (page 9, first paragraph), 10,000 daltons (page 8, paragraph 0035), 12,000 daltons (Example 6.c.), and 20,000 daltons (Example 6.d.).

No new matter has been added to the claims by virtue of the amendments presented herein.

III. Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1-3, 6-19, 21, 23, 24, 26, and 27 under 35 U.S.C. §112, second paragraph. The Examiner has asserted that the subject claims are indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Specifically, it is the Examiner's position that the phrase, "wherein said conjugate is absent non-covalent bonds" remains indefinite as to what is being claimed.

In response thereto, this language has been deleted from claim 1.

In view of the amendment to claim 1, withdrawal of the rejection of the claims under 35 U.S.C. §112, second paragraph, is respectfully requested.

IV. Prior Art Rejections: Rejections Under 35 U.S.C. §103

A. GROUNDS OF REJECTION.

The Examiner has maintained his rejection of claims 1-3, 5-19, 21, 23, 26, and 27 under 35 U.S.C. §103(a) as unpatentable over Delgado, et al., and Wu, et al.

Specifically, the Examiner has maintained his position, that, based upon the teachings of Delgado and Wu, it would have been obvious at the time of the invention to arrive at a peptide that is either biphalin or DPDPE, covalently attached to a water soluble polymer such as those recited in claim 1, to provide a hydrophilic conjugate capable of transport across the blood brain barrier when administered to the blood circulation.

This rejection is respectfully traversed for the reasons which follow.

B. THE INVENTION

The present invention is directed to hydrophilic polymer conjugates capable *per se* of transport across the blood brain barrier. A conjugate of the invention is characterized as either biphalin or DPDPE, covalently linked to a water-soluble polymer having a molecular weight between about 2,000 and 100,000 daltons (specific polymers are recited in Claim 1). The invention is surprising since, prior to the invention, it was believed that large hydrophilic polymers such as PEG, when attached to a peptide capable of crossing the BBB, would interfere with the transport of such peptides across

the BBB. Moreover, it was further believed that such covalent attachment would impair the interaction between the peptide and its receptor.

C. CITED ART

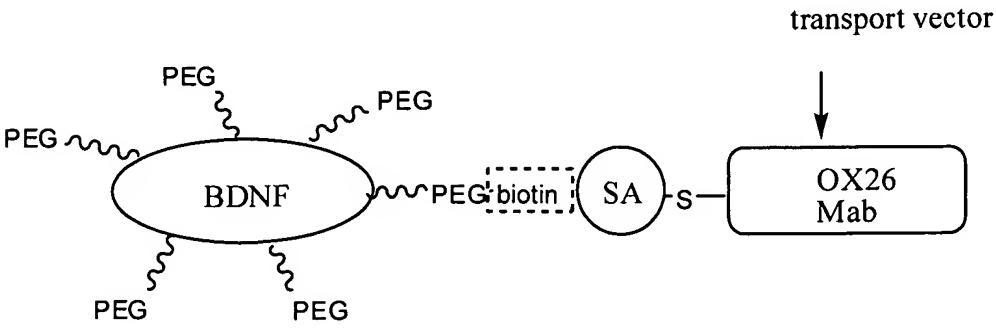
Delgado, et al. and Wu et al. have been extensively characterized in Applicant's previous Amendment dated November 17, 2006. These characterizations are not repeated here. However, the main points of each reference relied upon by the Examiner, as well as their shortcomings with respect to rendering obvious the Applicant's claimed invention, are touched on below.

Delgado et al. Deldado provides a review of PEG-*protein* conjugates prepared up until 1992. Specifically, Delgado describes the generic benefits of PEGylation, as well as the chemical, immunologic, pharmacokinetic, and pharmacodynamic properties of several specific proteins (aspariginase, uricase, superoxide dismutase, lactoferrin, etc.), as well as applications thereof. Delgado describes various chemical approaches for coupling PEG to a protein, as well as characterization of the resulting protein conjugates.

Delgado is nothing more than a general review article related to the PEGylation of *proteins*. Delgado is not directed to peptides, nor to PEGylation of peptides, as in the case of the instant invention. Delgado fails to suggest PEGylation of biphalin or DPDPE, for crossing the blood brain barrier or for any other purpose.

In sum, when considered as a whole, in no way is Delgado directed to the problems addressed by the current invention (the problem of transport of an analgesic peptide such as DPDPE or biphalin crossing the blood brain barrier), nor does Delgado even remotely suggest the solution provided by the Applicants (namely, PEGylation of an analgesic peptide such as DPDPE or biphalin). Thus, there can be no motivation for one skilled in the art to even look to Delgado. Moreover, even if one skilled in the art were to look to Delgado, Delgado fails to provide even the slightest motivation for one to PEGylate a peptide such as either biphalin or DPDPE, for any reason, let alone to arrive at a conjugate capable of transport across the BBB.

Wu et al. Wu describes modification of brain-derived neurotrophic factor (BDNF) to provide a conjugate capable of transport across the BBB upon peripheral administration.



The key features of Wu are as follows:

1. Wu describes a 3-component transport system of BDNF. BDNF is a neurotrophic factor – that is to say, a protein. Specifically, BDNF is a 27.0 kDa dimer formed by two identical 119 amino acid subunits. In contrast, the claimed invention is directed to small *peptides* of less than ten amino acids – specifically, biphalin and DPDPE. Conjugates of proteins and of peptides are completely different molecular entities, as are the problems associated therewith – e.g., the synthetic approach of covalently attaching a polymer such as PEG to a protein versus a peptide, bioactivity of the respective conjugates, chemical and pharmacological properties of the resulting conjugates, purification thereof, etc.

2. Wu teaches that for neurotrophic factors to have therapeutic value in humans, the neurotrophic factor must be conjugated to a BBB (blood brain barrier) delivery system that enables transport across the BBB after peripheral administration (Wu, page 254, column 1, last paragraph), as well as have optimized pharmacokinetics. In the delivery system of Wu, the component described to provide transport across the BBB is the OX26 murine mAB (Wu, page 254, column 2). Wu teaches that the OX26 murine mAB is an *essential feature* for providing transport of the BDNF across the BBB – a feature which is absent from the Applicant's claims.

In sum, when considered as a whole, Wu is directed to transport of neurotrophic factors such as BDNF across the BBB to result in neuroprotection. Wu fails to teach or suggest conjugate formation of *any* peptide, let alone DPDPE or biphalin. Moreover, nowhere does Wu suggest modifying the teachings therein to eliminate the transport vector component to provide a conjugate of any protein (or even peptide for that matter) for transport across the BBB – since to do so would be to eliminate a critical feature of Wu.

D. ARGUMENT

To establish a prima facie case of obviousness, three basic criteria must be met.

First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

Second, there must be a reasonable expectation of success.

Finally, the prior art reference (or references when combined) must teach or suggest *all* the claim limitations.

Moreover, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

The Cited Art Fails to Teach or Suggest all Claim Limitations.

The art relied upon by the Examiner, when considered either singly or in combination, fails to teach covalent attachment of a water-soluble polymer such as PEG to *any* peptide, let alone to a neuropeptide such as biphalin or DPDPE. In particular, Delgado describes PEGylation of proteins, while Wu describes a particular three-component delivery system for BDNF. And while the Examiner properly notes that Wu suggests that there are over 30 known neurotrophic factors that may prove to be powerful neuropharmaceuticals should they be reformulated in a manner such as BDNF (Wu, page 258, final paragraph) – a neurotrophic factor is completely different from a neuro*peptide* such as biphalin or DPDPE.

In sum, Delgado and Wu, when considered in combination, fail to suggest a hydrophilic conjugate comprising a water-soluble polymer of the type encompassed by the Applicant's claims conjugated to either biphalin or DPDPE.

The Cited References Fail to Provide Motivation to Modify

"The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ 1313, 1317 (Fed. Cir. 2000), *In re Lee*, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34.

Neither Delgado nor Wu, when considered either singly or in combination, provide the slightest motivation to modify the teachings therein to arrive at the Applicant's claimed invention. Specifically, nowhere does Delgado suggest PEG conjugation to a peptide of any sort, let alone to biphalin or to DPDPE. Nor does Delgado address the problem of arriving at neuro*peptide* compositions capable of crossing the blood brain barrier. The same applies to Wu. Wu teaches a three component system of BDNF capable of transport across the BBB. Wu is not directed to transport of *peptides* across the BBB, nor does Wu provide any mention of biphalin nor of DPDPE. Nowhere does Wu provide the slightest motivation to modify the teachings therein to arrive at the Applicant's claimed invention. That is to say, nowhere does Wu:

- provide the slightest motivation to modify or substitute BDNF with a small neuro*peptide* such as biphalin or DPDPE,
- teach a conjugate in which a peptide such as biphalin or DPDPE is conjugated solely to a water-soluble polymer such as PEG, *and* is capable of transport across the BBB.

A prior art references must be considered in its entirety, i.e., as a whole, *including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983).*

In fact, when considered as a whole, Wu actually teaches away from the Applicant's claimed invention, since Wu teaches that in order for a neurotrophic factor such as BDNF to cross the blood brain barrier, it must not only be modified to possess

optimized plasma pharmacokinetics (e.g., via covalent attachment to PEG), but *must* also be conjugated to a transport vector such as OX26 mAB. To modify the teachings of Wu to arrive at the claimed invention, one would have to eliminate a feature of Wu stated to be critical for transport of BDNF across the BBB (i.e., the transport vector). Since the modification proposed by the Examiner, i.e., the elimination of the transport vector, would change the principle of operation of the system described by Wu, and according to Wu, render it inoperable for transport across the BBB, then the teachings of this reference, even when combined with Delgado, are not sufficient to render the instant claims obvious.

No Reasonable Expectation of Success

One additional criterium for establishing a prima facie case of obviousness is that the prior art at the time of the invention must provide a reasonable expectation of success – a criterium that is clearly not met when considering, as a whole, the references relied upon by the Examiner.

In the summary (page 258, final paragraph), Wu states that neurotrophic factors may prove to be powerful neuropharmaceuticals if they are reformulated such as BDNF – both to enable transport across the BBB (e.g., via a transport vector) and to optimize plasma pharmacokinetics (e.g., by attachment to PEG). As discussed previously, based upon the teachings of Wu, one skilled in the art would not expect a conjugate such as that embodied by the Applicant's claims to be capable of transport across the BBB, since it is absent a transport vector component stated by Wu to be critical for such transport.

It is submitted that based upon the arguments and supporting case law provided above, the Examiner has failed to establish a case of prima facie obviousness for the subject claims.

In view of the above, it can hardly be stated that, at the time of the invention, it would have been obvious (in the absence of the teachings of the Applicant's disclosure) that mere PEGylation of a peptide such as DPDPE or biphalin would result in a conjugate capable of transport across the blood brain barrier.

In sum, it is submitted that the pending claims comply with the standards of 35 U.S.C. §103. Withdrawal of the rejection of the claims under 35 U.S.C. §103 is therefore respectfully requested.

V. Conclusion

In view of the foregoing, the Applicant submits that all of the claims pending in the application meet the standards of 35 U.S.C. §112 and patentably define over the cited art. A Notice of Allowance is therefore respectfully requested.

If a telephone conference would expedite the prosecution of the subject application, the Examiner is requested to call the undersigned at (650) 838-4406.

Respectfully submitted,
Perkins Coie LLP

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